REMARKS

After entry of the present amendment, claims 10-12, 16-24, and 33-38 will be pending and under consideration. In the present communication, claims 13, 14, and 15 have been cancelled without prejudice, claims 10, 16-18, and 24 have been amended, and claims 33 to 38 have been added. A marked up copy to show changes made is attached herewith as Exhibit A. All the pending claims under consideration, after entry of the present amendment are attached herewith as Exhibit B.

No new matter is added by the present amendments and added claims. For example, the amendments to claim 10 and 24 are supported by Table 5 (page 39) and Figure 4. The amendment to claims 16-18, as well as newly added claims 33 to 38 are supported by the disclosure, for example at page 24, line 11, to page 28, line 27. Applicant respectfully requests reconsideration of the present application.

Claim Objections

The Office Action objects to claim 13 alleging that it does not further limit claim 11. Claim 13 has been cancelled. As such, Applicant respectfully request withdrawal of the claim objection.

Rejection Under 35 U.S.C. § 112, Enablement

Claims 10 and 13-24 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Applicant respectfully traverse the rejection.

The Office Action alleges that the present invention is not enabled because the claimed invention is overly broad in being directed to identifying any cellular proliferative disorder, and

to any CpG island within the recited genes. Furthermore, the Office Action asserts that it is unpredictable which CpG islands, and which subregions within those islands, are associated with various tissues based on cited published reports, for example related to acute myelogenous leukemia (AML) (Toyota et al., Blood, Vol. 97, 2823 (2001)), and results of the present specification, which indicate that the hypermethylated gene CACNA1G, is not hypermethylated in all cell proliferative disorders. Finally, the Office Action alleges that the present invention is not enabled because experimental details are not presented regarding the correlation of hypermethylation and cellular proliferative disorders for all of the recited genes, except CACNA1G.

The CCPA stated that, "there is no magical relation between the number of representative examples and the breadth of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode contemplated'." (In re Borkowski and Van Venrooy, 164 USPQ 642, 646 (C.C.P.A., 1970)). The specification recites the nucleotide sequence of a CpG island for 14 different genes, as recited in claim 10, and for each of these genes, discloses at least one type of cancer in which the recited CpG island is hypermethylated (see specification, Table 5). The specification discloses methods and probes that teach a skilled artisan how to make and use the present invention.

Regarding the term "cellular proliferative disorder," the term has been removed from claim 10, but included in newly added claim 33, which is directed to examining the CpG island of CACNA1G. As taught in the specification, the CpG island of CACNA1G is hypermethylated in numerous cancers and cellular proliferative disorders, including colorectal cancer, colorectal adenomas, gastric cancers, and AML, but not in normal tissue (See e.g., page 27, lines 204, and page 24, lines 28-29). It is noted that subregions 1 and 2 of the CACNA1G CpG island do not appear to be hypermethylated in gliomas. However, the specification provides data

demonstrating that CACNA1G is hypermethylated in at least 3 different cancers and 1 benign condition. Applicant points out that it is not necessary to demonstrate that the CACNA1G CpG island is hypermethylated in every cellular proliferative disorder in order to enable the invention. As illustrated in the specification, CACNA1G hypermethylation occurs in many cellular proliferative disorders. Therefore, the specification supports newly added claim 33 which is directed to "cellular proliferative disorders."

Toyota et al. (Blood, Vol. 97, 2823 (2001)) is cited in the Office Action as indicating that CACNA1G is not hypermethylated in AML. However, this reference actually illustrates the association between CACNA1G and AML. For example, Toyota et al. report that no significant methylation of CACNA1G was observed in *normal* bone marrow. However, in AML, some patients have CACNA1G methylation densities above 10% (See Table 2 of Toyota et al.). Statistical conclusions in Toyota which are cited in the Office Action, were not based on the entire population of patients, but only a subset of patients that did not include those with the highest degree of hypermethylation, and were not directed at the correlation between hypermethylation of CACNA1G and AML. Rather the statistical analysis focused on the association of methylation of CACNA1G and methylation of the estrogen receptor (page 2826, right column).

In summary, the claimed inventions of the pending claims are enabled by the disclosure as filed. Therefore, Applicant respectfully request removal of the rejection of claims 10, and 13-24 under 35 U.S.C. § 112.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance and a notice to that effect is respectfully requested. The Examiner is invited

to contact Applicant's undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: August 15, 2002

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Enclosures: Exhibits A and B

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EXHIBIT A: CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Please cancel claims 13, 14, and 15 without prejudice.

Please amend the claims as follows:

10. (Twice amended) A method for detecting a [cellular proliferative disorder] cancer associated with APOB, CACNA1G, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4 comprising:

a) contacting a nucleic acid-containing specimen from a subject with an agent that provides a determination of the methylation state of at least one CpG island of a gene or associated regulatory region of the gene;

wherein the gene is selected from the group consisting of APOB, CACNA1G, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1, SDC4 and combinations thereof and

b) detecting [aberrant methylation] hypermethylation of a region of the gene or regulatory region, wherein hypermethylation of a region as compared to the same region of the gene or associated regulatory region in a subject not having said [cellular proliferative disorder] cancer is indicative of [a cellular proliferative disorder] the cancer.

16. (Amended) The method of claim [15] 33, wherein the regions comprise regions 1-2 of CACNA1G.

17. (Amended) The method claim [15] 33, wherein the regions comprise regions 5-7 of CACNA1G.

18. (Amended) The method claim [15] 33, wherein the regions comprise regions 3, 4 and 8 of CACNA1G.

24. (Amended) The method of claim 10, wherein said cancer is selected from the group consisting of astrocytoma, [anaplastic astrocytoma], glioblastoma, medulloblastoma, gastric cancer, colorectal cancer, [colorectal adenoma], acute myelogenous leukemia, lung cancer, renal cancer, leukemia, breast cancer, prostate cancer, endometrial cancer and neuroblastoma.

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EXHIBIT B: CLAIMS AS THEY WILL STAND UPON ENTRY OF THE AMENDMENT

10. (Twice amended) A method for detecting a cancer associated with APOB, CACNA1G, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4 comprising:

a) contacting a nucleic acid-containing specimen from a subject with an agent that provides a determination of the methylation state of at least one CpG island of a gene or associated regulatory region of the gene;

wherein the gene is selected from the group consisting of APOB, CACNA1G, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1, SDC4 and combinations thereof and

b) detecting hypermethylation of a region of the gene or regulatory region, wherein hypermethylation of a region as compared to the same region of the gene or associated regulatory region in a subject not having said cancer is indicative of the cancer.

16. (Amended) The method of claim 33, wherein the regions comprise regions 1-2 of CACNA1G.

17. (Amended) The method claim 33, wherein the regions comprise regions 5-7 of CACNA1G.

18. (Amended) The method claim 33, wherein the regions comprise regions 3, 4 and 8 of CACNA1G.

19. The method of claim 10, wherein the agent is a pair of primers that hybridize with a target sequence in the gene or associated regulatory region of the gene.

20. The method of claim 19, wherein the primers hybridize with a target polynucleotide sequence having the sequence selected from the group consisting of SEQ ID NO:55-103 and SEQ ID NO:104.

21. (Amended) The method of claim 20, wherein the primer pair is selected from the group consisting of SEQ ID NO:1 and 2, SEQ ID NO:3 and 4, SEQ ID NO:5 and 6, SEQ ID NO:7 and 8, SEQ ID NO:9 and 10, SEQ ID NO:11 and 12, SEQ ID NO:13 and 14, SEQ ID NO:15 and 16, SEQ ID NO:17 and 18, SEQ ID NO:19 and 20, SEQ ID NO:21 and 22, SEQ ID NO:23 and 24, SEQ ID NO:25 and 26, SEQ ID NO:27 and 28, SEQ ID NO:29 and 30, SEQ ID NO:31 and 32, SEQ ID NO:33 and 34, SEQ ID NO:35 and 36, SEQ ID NO:37 and 38, SEQ ID NO:39 and 40, SEQ ID NO:41 and 42, SEQ ID NO:43 and 44, SEQ ID NO:45 and 46, SEQ ID NO:47 and 48, and SEQ ID NO:49 and 50.

22. The method of claim 10, wherein the nucleic acid-containing specimen comprises a tissue selected from the group consisting of brain, colon, urogenital, lung, renal, prostate, pancreas, liver, esophagus, stomach, hematopoietic, breast, thymus, testis, ovarian, and uterine.

23. The method of claim 10, wherein the nucleic acid-containing specimen is selected from the group consisting of serum, urine, saliva, blood, cerebrospinal fluid, pleural fluid, ascites fluid, sputum, stool, and biopsy sample.

24. (Amended) The method of claim 10, wherein said cancer is selected from the group consisting of astrocytoma, glioblastoma, medulloblastoma, gastric cancer, colorectal cancer, acute myelogenous leukemia, lung cancer, renal cancer, leukemia, breast cancer, prostate cancer, endometrial cancer and neuroblastoma.

33. A method for detecting a cellular proliferative disorder associated with hypermethylation of CACNA1G, the method comprising contacting a nucleic acid-containing specimen from a subject with an agent that provides a determination of the methylation state of a CACNA1G CpG island comprising any of SEQ ID NO:35-42, wherein hypermethylation of the CACNA1G CpG island is indicative of the presence of the cellular proliferative disorder, thereby detecting the cellular proliferative disorder.

34. The method of claim 33, wherein the CpG island comprises SEQ ID NO:35, 36, 39, 40 and 41.

35. The method of claim 33, wherein the agent is a primer pair that hybridizes to the CACNA1G CpG island.

36. The method of claim 35, wherein the primer pair is selected from SEQ ID NO:33 and 34; SEQ ID NO: 35 and 36; SEQ ID NO:37 and 38; SEQ ID NO:39 and 40; SEQ ID NO:41 and 42; SEQ ID NO: 43 and 44; SEQ ID NO: 45 and 46; SEQ ID NO:47 and 48; and SEQ ID NO:49 and 50.

37. The method of claim 33, wherein the cellular proliferative disorder is colorectal cancer, colorectal adenoma, gastric cancer, lung cancer, breast cancer, hematopoietic tumors, prostate cancer, or acute myeloid leukemia (AML).

38. The method of claim 33, wherein the cellular proliferative disorder is astrocytoma, glioblastoma, medulloblastoma, lung cancer, renal cancer, endometrial cancer or neuroblastoma.